Division of Research Services FY 1986 Annual Report

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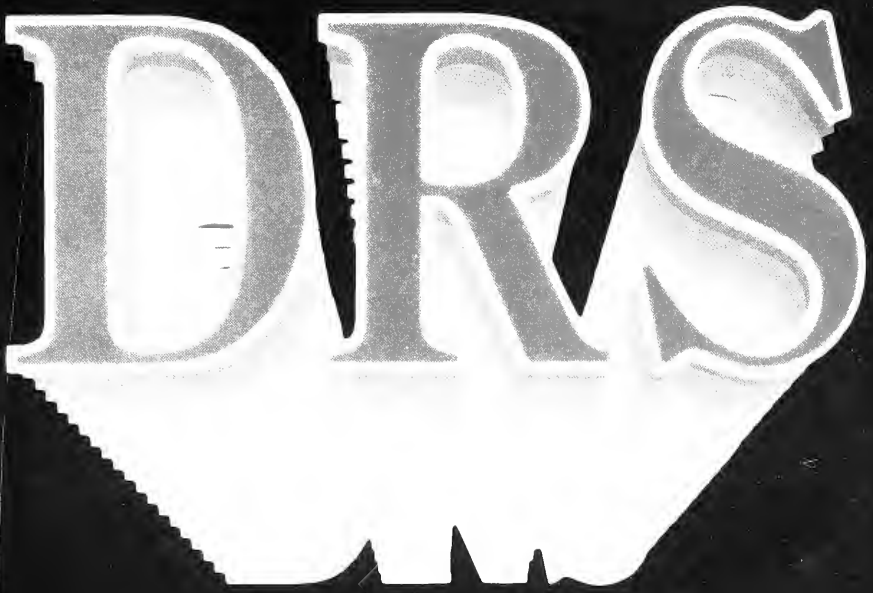
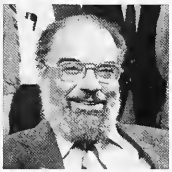


30 Years of Service

Division of Research Services

FY 1986 Annual Report



Dr. Robert A. Whitney, Jr., Director, Division of Research Services, with the DRS Branch Chiefs. *Left to right*: Dr. Stephen Potkay, Veterinary Resources Branch; Dr. Murray Eden, Biomedical Engineering and Instrumentation Section; Jane Leitch, Executive Officer, DRS; Carolyn P. Brown, Library Branch (the NIH Library); Ronald B. Winterrowd, Medical Arts and Photography Branch.

A Letter From the Director

Robert A. Whitney, Jr., D.V.M.,
Director
Division of Research Services
National Institutes of Health

As NIH began its centenary year in October 1986, the Division of Research Services was nearing the end of its 30th anniversary year. Joining with the other Bureaus, Institutes, and Divisions in celebrating NIH's myriad contributions to human health, we also celebrate the constant support DRS personnel have given to the research that produces those contributions—support ranging from outright scientific collaboration to routine supplying of requisites for research.

The Division of Research Services began operations in January 1956 under its first Director, Chris Hansen, "to centralize and broaden services in support of research, in order to meet the needs of an expanding NIH program" (First Annual Report).

DRS now has four branches: Biomedical Engineering and Instrumentation (BEIB), Medical Arts and Photography (MAPB), NIH Library, and Veterinary Resources (VRB). Since they perform essential roles in the planning, performance, and reporting of biomedical research, they had all existed as NIH units under various names for many years before 1956. The NIH Library was established in 1903 as the library of the Hygienic Laboratory. Since the Laboratory's work was based on the example of Pasteur and Koch, animal experimentation was included from the first, and historical records show that good treatment of the animals was emphasized early on. The Laboratory had an artist on staff at least by 1913. By then, scientific instruments were probably already being modified or created for the particular needs of various labs.

DRS originally had five branches, formed from units of the Office of the Director, NIH: Laboratory Aids, Scientific Reports, Biometrics, Plant Engineering, and Sanitary Engineering.

The four current DRS branches developed from two of the original branches. VRB and BEIB were derived from the Laboratory Aids Branch; MAPB and the NIH Library came from the Scientific Reports Branch.

BEIB developed from the Instrument Section of the Laboratory Aids Branch. Because the section was providing investigators with increasingly varied and more sophisticated instrumentation services, it was elevated to branch status in 1960 as the Instrument Engineering and Development Branch. With more professional engineers and physical scientists on its staff, the new branch increased its collaborative research while continuing its technical services to NIH investigators; its name was changed to Biomedical Engineering and Instrumentation in 1965 to express its broader functions.

The Laboratory Aids Branch—minus BEIB—was renamed Veterinary Resources Branch in 1972, to reflect its primary functions of providing NIH investigators with animal models and the facilities and services related to using them.

The Library Branch and the Medical Arts and Photography Branch were formed in 1960 when the Scientific Reports Branch was dissolved; its other sections (much involved with Institute information offices) were transferred to what is now the Office of Communications, OD.

NIH intramural programs developed and expanded rapidly in the years after DRS was formed. The Division's three other original branches became the nuclei of NIH Divisions established later: the Division of Computer

Division of Research Services FY-86 Budget (in thousands of dollars)

Branch	Management	Service & Supply	Total
Veterinary Resources	$ 6,873	$ 8,887	$15,760
Biomedical Engineering & Instrumentation	4,081	8,443	12,524
Library	3,234		3,234
Medical Arts & Photography		7,062	7,062
Total	$14,188	$24,392	$38,580

Research and Technology (from Biometrics Branch, which had been renamed "Computation and Data Processing Branch"), Division of Engineering Services (from the Plant Engineering Branch and two other DRS branches developed later), and Division of Safety (from Sanitary Engineering Branch and later DRS components).

The various reorganizations have given DRS a sharper definition and goal. Beginning in 1962, DRS Annual Reports divided the Division's programs into two broad classifications: "Programs in direct support of research" and "Programs related to NIH facilities and environment." Since the 1981 reorganization, DRS has consisted entirely of branches whose activities had always been listed in the first category: direct support of research. DRS and its branches support research projects throughout their planning (NIH Library), performance (VRB, BEIB), and reporting (MAPB). Many NIH research projects require the support of all four branches.

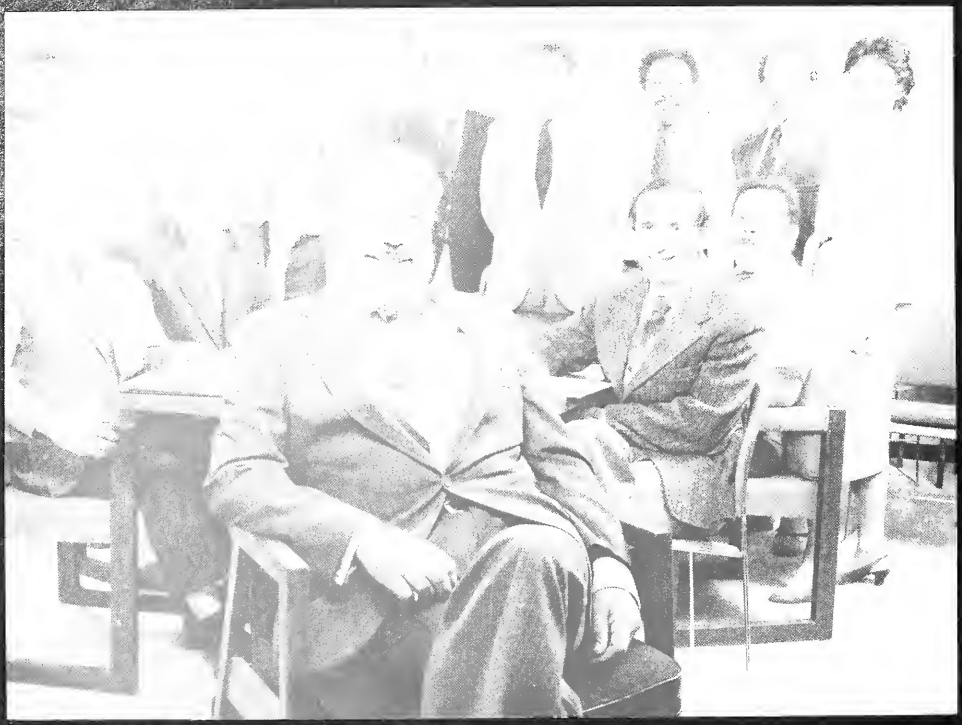
Under the direction of Chris Hansen and my other predecessors as Director of DRS—Dr. William B. DeWitt, Dr. Roger D. Estep, and Dr. Joe R. Held—the Division has made many changes and adaptations to match changing needs in biomedical research. The following Branch reports show that this spirit of innovation continues.

The Division of Research Services

The many specialized functions of the Division are designed to support all of the 18 Bureaus, Institutes, and Divisions (BIDs) which constitute the National Institutes of Health. The primary program emphasis, however, is directed at serving the 8,000 staff members of the intramural program, including more than 2,600 doctoral level scientists who conduct research in NIH laboratories.

Organizationally, the Division is structured to provide products and services in support of the sequential steps in every biomedical research project: planning, making available models and substrates, manipulating and measuring research materials, and recording and communicating research results.

- The Library Branch possesses or has access to virtually all published biomedical knowledge to assist the investigator in planning and designing his/her project.
- The Veterinary Resources Branch provides the animal models, organic materials, and proper facilities for their use.
- The Biomedical Engineering and Instrumentation Branch collaborates with the investigator in devising the means whereby research materials may be manipulated and results measured, often with highly sophisticated electronic equipment.
- Finally, the skills of the Medical Arts and Photography Branch are available to all investigators to enable them to record the results of their research and communicate them to the scientific community.



Dr. Murray Eden, Chief, Biomedical Engineering and Instrumentation Branch, DRS, with his supervisory staff. *Seated, l to r:* Walter S. Friauf, Electrical and Electronic Engineering Section; William Schuette, Applied Clinical Engineering Section; Dr. Seth Goldstein, Mechanical Engineering Section; Nelson Smith, Deputy Assistant Chief for Scientific Equipment Services. *Standing:* Howard Metz, Assistant Chief for Scientific Equipment Services; William V. Sweeney, Jr., Clinical Care Instrumentation Section (acting); John Mason, Mechanical Instrumentation Fabrication Section; Lewis E. Cascio, Research Instrumentation Section; Dr. Henry S. Eden, Deputy Branch Chief and Chief, Electron Beam Imaging and Microspectroscopy Group; Dr. David Hoult, Nuclear Magnetic Resonance Imaging Group; Roland Corsey, Chairperson, BEIB Human Relations Advisory Committee; Robert L. Dedrick, Chemical Engineering Section; Dr. Marc S. Lewis, Analytical Methods Group (representing Dr. Andre F. LeRoy); Marie C. Gavin, Material and Clerical Operations Section.

Biomedical Engineering and Instrumentation Branch

Murray Eden, Ph.D., Chief

Chemical and mechanical separation techniques are part of the warp and woof of biomedical research. In their best known application these methods are used to isolate and purify substances, based upon differences in physical properties, such as solubility, volatility, mass, particle size, adsorption, or electrical charge. In some cases, however, the techniques can be purely analytical, without isolation of substances; a particularly elegant example is analytical ultracentrifugation.

Analytical Ultracentifugation in BEIB

Among its many activities the Biomedical Engineering and Instrumentation Branch (BEIB), NIH's focal point for engineering and related sciences, collaborates in research to develop new methods of applying analytical ultracentrifugation in the measurement of masses and concentrations in mixtures of macromolecules. The analytical ultracentrifuge permits application of a precisely controlled centrifugal field to a solution containing the macromolecular components. The field—as much as one-half million g's—causes the molecules in solution to sediment toward the bottom of an ultracentrifuge cell.

As the concentration of molecules increases toward the bottom of the cell, they tend to diffuse back toward the region of lower concentration. When an equilibrium is reached there is an exponential gradient in concentration for each macromolecular species present in solution. The rate of change of the gradient for a particular molecule depends essentially upon the strength of the applied centrifugal field and the mass of the molecule.

In a given centrifugal field light molecules will have shallow concentration gradients, while heavy molecules will have steep gradients. The centrifuge records these gradients by measuring ultraviolet light absorption along the length of the ultracentrifuge cell.

BEIB can accurately determine the molecular mass of a single component in solution or resolve the sums of the exponential distributions that result when more than one molecular species is present by using a nonlinear model to fit the data. As must be expected, however, when the number of components increases, the accuracy of the determination of masses and relative concentrations decreases. (When the number of molecular species present is very large, as in the case of a biopolymer, only an approximation of relative concentration as a function of molecular mass is possible. This is a very difficult problem, however, and no other analytical method does significantly better.)

BEIB is also applying its expertise to collaborative studies of systems of macromolecules that interact with each other. Examples include work with the National Institute of Dental Research (NIDR) on the association of fibrinogen with clotting Factor XIII from plasma and platelets, along with work on the association of plasminogen with the D and E fragments of fibrinogen, and work with the National Cancer Institute (NCI) on the associative properties of cell adhesion peptides.

The combination of analytical ultracentrifugation with mathematical modeling is a powerful tool. It has the added advantages of requiring very small amounts of sample and being able to deal with molecular masses over a wider range of sizes than any other method. Making such measurements over a range of temperatures permits the calculation of various thermodynamic parameters, which can then characterize different forces and mechanisms involved in molecular interactions. BEIB is collaborating in this area, for example, on work with the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) on the thermodynamics of the association of subunit chains of the toxic protein ricin and the relationship of this association to cellular toxicity.

Over the years BEIB has had occasions to collaborate on the development and refinement of separation technologies of many forms—not surprisingly so, given the ubiquity and importance of these techniques in the research environment. Examples have included design of multi-laser flow cytometers; methodologies for liquid chromatography employing reductive electrochemical detection; filtration systems for continous plasma sampling; and methods for separating cholesterol from blood. These topics and others will be the subject of future annual reports.

BEIB in FY 1986

BEIB has also been busy fulfilling its commitment to provide the NIH research community with a broad range of scientific and engineering expertise. For example, BEIB has collaborated in more than 200 projects to produce advanced instrumentation, models, methods, and techniques dedicated to the acquisition of biomedical information previously unavailable to NIH's scientists.

The staff of more than 40 professional physical scientists and engineers and 80 technical support personnel responded to over 2500 requests for the fabrication and modification of laboratory devices and made another 9000 repairs and minor changes to scientific equipment.

BEIB's professional staff functions within four sections and the Office of the Chief. Here is a brief description of their activities in FY 1986.

Applied Clinical Engineering Section (ACES)

The ACES continues to support a variety of biomedical research throughout the NIH. The majority of its collaborations are located in the Clinical Center (CC), however, and relate directly to patient care. The remaining research projects are in areas where the Section has a particular expertise.

For example, the ACES has been working closely with operating room and intensive care unit clinicians to evaluate newly available equipment, such as disposable pressure transducers, defibrillators, and intravenous infusion pumps. The ACES and the Clinical Center Instrumentation Section (CCIS) are also responsible for the ongoing semiannual electrical safety inspection of all equipment used in the Clinical Center. (The Section played an important role in the acquisition of accreditation for the Clinical Center from the Joint Commission on Accreditation of Hospitals.) The Section has also assisted the CCIS technicians in the design and installation of interface equipment for the newly renovated operating rooms. Moreover, ACES has developed a semiautomated pill-dispensing system that will allow certain patients to administer their own pain medication.

The Section has been active in several areas of clinical research involving sickle cell anemia. Laser Doppler flow technology is being used in the study of microcirculation in sickle cell patients under both normal and perturbed conditons. Hematological and cardiovascular variables are also being evaluated as risk factors for patients with sickle cell anemia.

The Section has developed a computer-based system for the evaluation of hemiparkinsonism in primates that uses an infrared position-detection method for measurement of preferential turning. A second computer-controlled system has been developed that measures the motor response of the primates to food stimuli.

Laboratory instrumentation developed by the Section includes a special-purpose, temperature-controlled device for rapid temperature cycling of cells, while monitoring the cells bioelectric activity. Additionally an in-vitro heat conduction calorimeter has been developed that uses tantalum chambers to contain solutions of cells. Fiber optic probes inserted into the chamber monitor pH, p02, and temperature, while the calorimeter measures heat production.

The ACES is collaborating with the Surgery Branch, National Heart, Lung, and Blood Institute (NHLBI), in a study of the effects of mitral valve replacement on left ventricular function. Groups of animals that have received replacement valves have been instrumented to monitor pressures in the left and right ventricles and the aorta. Mathematical theory was utilized to calculate left ventricular volumes, as well as midwall circumferences and stresses. This data, along with stroke volumes, fractional shortening in each of three dimensions, axial ratios, Lagrangian strains, and various systolic performance parameters (such as maximum systolic pressure and maximum dP/dt) will be compared between two groups of sheep: (1) those with defects in a mitral leaflet, surgically induced six months prior to valve replacement, and (2) those with normal valves at the time of valve replacement

Chemical Engineering Section

The Chemical Engineering Section provides consultative and collaborative support to the NIH in transport phenomena, pharmacokinetics, fluid mechanics, biomaterials and instrumentation. Traditionally the assessment of diabetic retinopathy has been by the leakiness of retinal blood vessels to the fluorescent dye fluorescein. This method is largely subjective. The Section has developed a mathematical model to describe the movement of fluorescein from the blood through the blood-retinal barrier and into the vitreous. A commercially available instrument is able to measure profiles of fluorescence in the vitreous, but finite sampling volumes distort the measured profile. A method of analysis has been developed in BEIB that simulates the output of the instrument by spatially averaging vitreal fluorescein concentration profiles calculated from the mathematical model. The blood-retinal barrier permeability and the dye diffusivity in the vitreous can be obtained by comparing experimental data with model simulations. If the permeability can be shown to

correlate with the severity of disease, then this procedure will serve as a valuable tool both to screen for early detection and to monitor response to treatment.

In a related project, a fiber-optic probe has been used to measure the oxygen partial pressure in the vitreous near the retina of normal and diabetic dogs. The fiber-optic sensor, developed within the Section, is based on the principle of fluorescence quenching by oxygen. This provides an equilibrium measurement, rather than using the well-known polarographic approach. The in vivo measurements have been designed to evaluate the suitability of the sensor for studies of diabetic retinopathy in experimental animals and in human subjects.

Calculation of the pharmacokinetic advantage of regional drug administration requires knowledge of relevant intercompartmental transport parameters. In a lumped model such a parameter is the blood (or plasma) flow rate for intra-arterial drug infusion or the permeability-area product for intraperitoneal or intrathecal administration. We have examined the way in which these parameters vary among mammalian species. It appears that the perfusion of many tissues and the intrinsic permeability of the peritoneal surface or the brain-cerebrospinal fluid interface are similar among mammals. This provides a clear basis for interspecies scaling based on organ size or surface areas. Intra-arterial or intrathecal treatment of the brain or meninges is a particularly interesting problem because of the relatively large brain of humans and because increased folding results in a cortical surface area that is almost proportional to brain size. Major unresolved issues remain concerning the distributed character of processes such as streaming of drug infused into an artery and nonuniform mixing of cerebrospinal fluid.

The pharmacokinetic advantage of intra-arterial drug administration can be increased if blood from the infused region is passed through an extracorporeal device that removes drug before the blood is returned to the body. This concept was further validated in the clinic through use of such a device, when three patients were treated at twice the usual dose of drug, but experienced comparable or lower systemic drug exposure. Preliminary tests using infusions of a harmless dye showed the feasibility of the approach.

The Section has examined drug kinetics at the molecular level in studies of the reactions of cis-diamminedichloroplatinum (II) (DDP) and methotrexate (MTX). An improved high performance liquid chromatography and hanging mercury drop electrode technique have been used to follow the fate of DDP and its major hydrolysis products in various aqueous media. Peaks corresponding to two metabolites have been identified by using off-line fraction collection with platinum determination by atomic absorption methods; kinetic analysis of these platinum-containing peaks confirmed their identities.

Research during the past decade has shown that the antifolate effects of MTX are mediated by its polyglutamate metabolites. The polyglutamates are known to be responsible, directly or indirectly, for inhibition of both thymidylate and purine synthesis. The Section has formulated mathematically the polyglutamation kinetics of MTX in MCF-7 human breast cancer cells. The model accounts for glutamation and hydrolysis kinetics up through the pentaglutamate level, increased synthesis of dihydrofolate reductase following exposure to drug, reversible tight-binding to reductase, and membrane transport of all the drug polyglutamates. The glutamation, hydrolysis, and efflux parameters have been determined from fits to experimental MTX polyglutamate uptake and efflux data. The preferred substrate for folylpolyglutamyl synthase in the intact cell has been shown to be MTX diglutamate, on average being 2 to 3 times as reactive as either the parent drug or the triglutamate.

Work in experimental fluid mechanics has continued in the Section with further studies of mixing of solutions infused through intravascular catheters. Studies have included qualitative flow visualization experiments with infused dye solutions and quantitative determination of dye concentrations in distal branches of arterial models. Studies that were performed in a plastic model of the internal carotid artery and its major branches have been extended to a glass model of the hepatic arterial circulation. Streaming of dye and concomitant maldistribution in distal branches were observed when low infusion rates were used. Mixing was improved at higher infusion velocities or when injection of the dye solution occurred retrograde to the blood flow.

Work is continuing to develop techniques to improve mixing and assure uniform delivery of drug to all tumor-bearing regions and minimize toxicity that might result from streaming to normal tissues. One approach which was shown to improve mixing in the carotid artery model and in vivo studies is jetting at high velocity retrograde to the direction of blood flow. BEIB has invented a catheter that incorporates a flexible wire coil. The coil strengthens the catheter so that high pressures may be used for angiography. It also provides some torsional and longitudinal rigidity to assist in catheter

placement. The prototype catheter can be inserted over a guide wire and then the hole at the catheter tip can be occluded with a tethered ball to direct infusate through small lateral orifices to form retrograde jets. Thus the catheter can function similar to a conventional end-hole catheter or as a jet catheter, depending on the position of the ball valve.

Electrical and Electronic Engineering Section (EEES)

The objective of the Section is to bring the power of modern electronic technology to bear on the needs of biomedical research. A major trend in recent years has been the standardization of signal processing capability in the form of digital computers. In order to exploit the power and economy of this development the Section is incorporating dedicated computers into increasing numbers of instrumentation systems. A typical example is a speech and sound analysis system developed for the National Institute of Child Health and Human Development. A mini-computer was interfaced with a high speed analog-to-digital converter, an array processor (to do high speed spectral analysis), and a commercial speech analyzer. The resulting system, with appropriate software, provides unusual versatility, plus the ability to handle frequencies higher than those encountered in human communication, but which are important in studies of squirrel monkeys. Another large computer-based system designed by the EEES is a fermentor for the National Institute of Allergy and Infectious Diseases (NIAID). In this device a computer controls temperature and the addition of reagents while simultaneously monitoring various parameters to allow optimization of yield. The same general approach was used for two smaller systems; a commercial RS-232 interface was used between a personal computer and custom electronics that includes transducers, indicators, and controls.

Other computer-based systems include a flow cytometry system developed in collaboration with ACES for researchers in NIAID. This system is being used initially to identify different strains of the parasite T. Cruzi by measuring four parameters and for computerized data analysis. Another system for the National Heart, Lung, and Blood Institute uses a PC to track the movement of cells. Indeed, most of the projects described below include a computer, even though it may not be central to the system.

Electro-optics is another rapidly developing branch of electronic technology which is having a significant impact on biomedical research. One of the most exciting developments is photo-dynamic therapy (PDT, renamed from photo-radiation therapy last year) for control of localized tumors. It has been used successfully to treat certain superficial cancers that have not responded to chemotherapy or radiation. The method involves introduction of an appropriate photo-chemical, usually hematoporphyrin derivitive (HPD) at present, into the region of concern. Malignant cells retain more of the HPD than do healthy cells. After an interval of several hours the tumor-bearing region is illuminated with light. Singlet oxygen, generated in the presence of HPD, kills the cancer cells. In collaboration with the Radiation Oncology Branch and the Surgery Branch, NCI, its use is being extended to treatment of intra-abdominal and intra-thoracic tumors, particularly ovarian and lung cancers. Because of the strong multiple scattering properties of physiological materials, the illumination problem is difficult, and the Section has developed a new photon diffusion theory to aid the development of optimal illumination systems. In addition, techniques are being developed for dosimetric measurements of sensitizer concentration, light penetration, and singlet oxygen concentration within tissue. Laser angioplasty is another major electro-optic project, in collaboration with the Cardiology and Surgery Branches, NHLBI. During the past year a variety of laser-fiber-optic systems have been evaluated, with interest focussing particularly on new erbium laser-zirconium fluoride fiber systems. Operating in the infra-red region (2900 nm), instead of the UV where excimer lasers operate, extremely strong absorption by water confines the ablation to the tissue in direct contact with the tip of the fiber, thus improving control.

An intriguing offshoot from this project is the hot-tip catheter, which is an alternate approach to removing plaque deposits. In principle this is an extremely simple approach, but in practice it is not easy to get enough power, about 10 watts, through the catheter to the tip. Approaches which have been explored here or elsewhere include fiber optics, wire wound elements, electric arcs, miniature torches, and bulk semiconductor heaters; but all have serious problems. We are exploring semiconductor junction heaters, and have developed a PC-based control system for regulating temperature and measuring the thermal resistance encountered by the tip.

The Section is providing considerable support to the refinement of a picosecond laser spectrofluorometer in the Laboratory for Technical Development (LTD), NHLBI. Software and interfaces for a mini-computer allow control of monochrometers, multi-channel analyzers, and

the like, and collection and procesing of data. Work is under way to improve the excitation optical system, to refine timing resolution, and to incorporate new multi-anode proximity focussed microchannel plate photomultiplier tubes into the detection system. This one project involves computer hardware and software, automated control, ultra-high-speed analog and digital circuitry, low-level transduction, and laser optics, thus exemplifying the diversity of technology currently encountered.

A fluorescence microscope developed in collaboration with NHLBI has great potential for biochemical studies of physiological systems. An argon ion laser is used for excitation, together with an acousto-optic modulator for wavelength selection, while an image intensifier-vidicon combination is used for detection. This system configuation provides fast wavelength switching, high spatial resolution and linearity, and extreme sensitivity. Other electro-optic work includes continuing applications of laser Doppler velocimetry, developments in time-resolved fluorimetry, and low light level video systems.

An interesting sytem of a totally different character was developed to monitor the location of Alzheimer's disease patients in the Clinical Center. Patients wear a wrist watch modified to emit a radio signal that is modulated at a different frequency for each patient. Antennae near exit doors sense the approach of patients, causing the doors to be locked automatically; relevant data are logged by a PC.

EEES is involved with NINCDS and DCRT in exploring and developing the potential of magneto-encephalography (MEG) to localize epileptic foci and facilitate other neural studies. A commercial seven channel detection system has been received and checked out, but progress has been slowed by the need to relocate the MEG lab to the ACRF. While this is under way, efforts have been directed toward refining the spherical model now generally used to accomodate the departure from sphericity of the human head, investigating algorithms for correlating EEG and MEG data, and classifying and normalizing epileptic discharges.

A number of old projects continue to be supported and upgraded; notably the Section is increasing the count rate capability of the Neuro-PET scanner to accomodate animal studies at higher dosage levels of radionuclides. Several new areas are being considered for increased effort, the most interesting perhaps being cell electrofusion.

Mechanical Engineering Section (MES)

The Mechanical Engineering Section conducted a wide diversity of collaborations with scientists in NIH's intramural research program involving analytical and experimental studies and the development of specialized instrumentation. The multi-year effort in collaboration with the Radiation Oncology Branch, NCI, continues to make substantial progress in the development of equipment and protocols for regional, radio-frequency-induced hyperthermia, used as an adjunctive treatment for cancer. The goal is to gain a better understanding of electromagnetic and thermal processes in tissues and to improve the efficiency of systems under development. In order to predict the patterns of energy deposition and the resulting temperature distribution within tissues, the Section has employed a combination of techniques using large-scale computerized electromagnetic 'block models' and thermal 'finite-difference models.' In addition the Section has used temperature probes in amputated human legs to measure experimentally the thermal fields produced by different applicators. Significant heating was determined to take place in bone and fat, a fact that requires re-evaluation of current assumptions about heating in clinical situations. Investigations are in progress on techniques to overcome this problem by modifying the applicator to provide better beam steering by amplitude and/or phase shifting the individual dipole elements of the applicator. A computer-controlled clinical hyperthermia system is now being assembled and will be extensively tested on additional limbs and phantoms before human use.

A substantial effort continues in the area of cardiovascular dynamics. Major progress has been made in a theoretical model of myocardial blood flow and myocardial oxygen demand. This model will be coupled to an improved model of the ventrical, which now includes an isotropic component of elasticity, passive and active viscoelasticity and non-cylindrical geometry. In a collaboration with INSERM (the Institut National de la Sante et de la Recherche Medicale, France) work is being performed to determine the physiological relationships between phasic coronary arterial and venous pressure and blood flow, aortic input impedance and ventricular dimensions so that they can be compared with the developing theoretical model. A highly successful NIH-INSERM workshop was held in which various collaborative efforts were organized. Other areas being investigated are ultra-

sonic backscatter from the myocardium and wave propagation in arteries. In another theoretical biomechanics project, extensions of the mathematical model of the transduction process in the cochlea have been made. The processing of a single tone has been completed, and the effects of some of the system nonlinearities clarified.

Work has continued on developing and supporting additional clinical applications of the everting catheter. Miniature units of #2 French size have been custom made for use in the fallopian tubes for treating certain types of infertility. The everting element is now being bonded to polytetrafluoroethylene (PTFE) catheters so that the device can be used through an endoscope for various diagnostic procedures in collaboration with the Naval Medical Command, National Capital Region, Department of Gastroenterology. A study has been performed to evaluate the effectiveness of diastolically-phased, pulsed intra-arterial infusions as a means of overcoming non-uniform mixing due to the effects of streaming when chemotherapy is administered via catheters. A clinical angiographic infusion system has been modified to produce phased pulsing, and quantitative tests with various catheters have been performed in a flow visualization system. The success of this program has led to a series of in vivo arterial infusions to further study mixing. Clinical usage is anticipated.

The Section continued its innovations in a variety of areas of bioinstrumentation, including optical sensors for assessing the viability of teeth by measuring light absorption due to hemoglobin in dental roots, and detecting the presence of caries using fluorescense techniques; continuously monitoring growth of bacterial cultures in a fermenter; clinical methods for using ultrasound to measure arterial wave speed, phasic blood velocity, and vessel wall dilatation; and several instruments for molecular biology. In particular, a relatively low-cost computer-controlled instrument is being developed to scan tissue culture dishes in order to locate cell colonies that have been fluorescently labeled using genetic engineering techniques. The dishes are then scribed at the selected locations so the colonies can be removed and cloned. Another instrument under development will automatically put one-and-only-one cell into a titer dish well, which will increase efficiency over present methods. Work continues on a system for three-dimensional histological reconstruction involving a remotely-controlled miniature microtome located inside a scanning electron microscope (SEM). Other projects include an improved constant-shear-field apparatus for electron spin resonance (ESR) studies of blood cells, and a novel prosthetic urethral sphincter.

Analytical Methods Group

The Analytical Methods Group develops advanced physico-chemical methods for identifying, characterizing and quantitating constituents of biochemical and biological systems. These measurements are of fundamental importance in understanding the behavior of certain chemical species in the body. The presence of metallic elements may be associated with the existence of some disease state and be related to its cause, while in other cases a metal-complex preparation may be administered to treat a disease.

In collaboration with investigators in the National Institute of Mental Health (NIMH) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA), we are measuring concentration levels of vanadium in the blood and cerebro-spinal fluid of normal volunteers and patients exhibiting manic-depressive behavior. The concentration levels obtained are in the picogram-per-ml range. In collaborative research with NCI, we are developing a comprehensive understanding of the behavior of metal-complex-based anti-cancer drugs, such as Cisplatin, which contain several complexes of platinum in equilibrium.

Recent work includes development of techniques to fractionate complex chemical species of biologically important elements using chromatographic methods. The species are characterized using various physico-chemical techniques in order to develop a better understanding of their behavior and interactions in biological milieux. The species are quantitated using electrothermal atomization and atomic absorption spectrometry. In order to develop a more complete understanding of their interconversion, rates at which chemical transformations between chemical species occur are being measured under carefully controlled conditions. Studies are also being conducted to yield information on chemical equilibria between species. These studies emphasize the separations and quantitation of ultra-trace complex constituent species at the nanogram-per-ml range and picogram-per-ml range in biological systems.

Still other studies involve isolation and purification of enzyme preparations such as calmodulin or cyclic-AMP, where the need arises to establish purity and measure the effects of low concentrations of metal that make the enzyme molecules active. These studies involve measuring concentrations that may vary over

several orders of magnitude. This work is in collaboration with NHLBI and NIMH.

In collaboration with investigators at the Oscar Lambret Cancer Treatment Center in France a study has been conducted on the kinetics and uptake of platinum complexes in cultures of human respiratory tract tumors.

At the request of the French Commissariat a l'Energie Atomique (French Atomic Energy Commission), an assessment of their program in the life sciences and research and development in the biomedical field has been initiated. Several of their project activities could become areas of collaboration with research groups at NIH.

In work conducted in collaboration with NHLBI and NIMH in mass-spectrometry, the energy distribution of secondary ions has been studied on different matrices, and a computer system has been developed for secondary ion mass spectrometry (SEMS). The computer system controls the quadrupole mass-spectrometer of the SEMS system and scans the energies of the secondary ions. The goal is to use the system to produce images of biological specimens.

Research in the area of the physical chemistry of biological macromolecules has involved an extensive collaborative effort with several institutes within NIH. A manuscript written in collaboration with NINCDS on studies of the thermodynamics of the association of the subunit chains of the toxic protein ricin and the relationship of this association to cellular toxicity is now in press. Studies in association with NIDR on the association of Factor XIII from plasma and platelets have been completed; current work is directed toward studies of the association of plasminogen with the D and E fragments of fibrinogen and studies of the interaction of fibrinogen with other proteins involved in blood clotting and fibrinolysis. A manuscript done in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) concerning the mechanism of formation of clathrin baskets is now in press. Studies on improvement in instrumentation and methodology of analytical ultracentrifugation are continuing. Significant progress has been made in the area of mathematical modeling used for data analysis. This work has directly benefitted studies of the physical chemistry of macromolecules as described above.

Electron Beam Imaging and Microspectroscopy Group

The group has been expanding the capabilities of its computer-controlled analytical electron microscope and applying this technology to a number of collaborative projects. A greatly improved electron energy loss spectrometer has been recently added to the instrumentation, and for the first time this has permitted simultaneous computer-controlled acquisition of element-specific electron energy loss and energy dispersive x-ray signals, as well as the dark-field elastic signal characteristic of sample morphology. Further developments have also taken place in the processing of spectra and elemental images to improve quantitation.

In collaboration with the Laboratory of Cell Biology and Genetics, NIDDK, the Group has been determining the composition of secretory granules in adrenal chromaffin cells. Samples have been prepared by rapid freezing and ultracryomicrotomy. Ionic concentrations of potassium, calcium, sodium and chlorine were measured and compared with existing data from isolated chromaffin granules. Some information about the concentration of proteins, nucleotides, and catecholamines was also obtained. These data are relevant to understanding the physiology of resting chromaffin cells and the changes that occur when they are stimulated.

In collaboration with the Laboratory of Neurobiology, NINCDS, the Group has determined the elemental distribution of calcium and potassium in rapidly-frozen, cryosectioned mouse cerebellar cortex. Of particular interest was the identification of intracellular calcium stores possibly localized in the endoplasmic reticulum of Purkinje cell spines in repetitively-stimulated cortex. Calcium stores were not evident in the presynaptic nerve terminals of resting or stimulated cells. The results suggest fundamental differences between presynaptic and postsynaptic nerve endings with regard to the mechanisms of calcium mobilization and transport.

In collaboration with Pulmonary Branch, NHLBI, the Group has obtained electron energy loss (EELS) and energy dispersive x-ray (EDXS) spectral maps of elemental distributions in macrophages obtained by broncho-alveolar lavage from patients with silicosis, asbestosis, and coal miner's lung disease. Data were also obtained from alveolar macrophages in lung biopsies. The study is being used to correlate disease with the incidence of inclusions in the macrophages.

A study has been made in collaboration with researchers from the Biozentrum, University of Basel, Switzerland, to investigate the feasibility of low-dose, high-resolution electron energy loss mapping of two-dimensional membrane crystals. Experimental measurements and theoretical predictions show that averaging over ten thousand

unit cells should provide the distribution of phosphorous and nitrogen in the lipid and protein components respectively at a dose of about ten electrons per square angstrom.

The instrumentation of the Group also includes a 50 KeV electron beam microanalyzer, which is connected to the Group's laboratory computer. Using this device, the Group has collaborated with NINCDS to localize and image aluminum, silicon, magnesium, and calcium in the hippocampal region of brains of victims of Parkinsonian dementia, amyotrophic lateral sclerosis (ALS), and Alzheimer's disease. This effort has been highly successful; the group has produced clearly resolved images of the elements in neurons and axons.

We have begun an extensive collaboration with the National Cancer Institute to determine the ionic content of individual cancer and normal cells which have been cloned with the gene responsible for cystic fibrosis. In addition, we have collaborated with the Clinical Pathology Department of the Clinical Center in an effort to quantitate and image the magnesium content of individual lymphocytes.

Beginning in 1986 the Group will establish a joint electron microscope facility with the National Bureau of Standards. The principal instrument will be a high-resolution field emission scanning transmission electron microscope (FESTEM). It is anticipated that this instrument will enable production of two-dimensional maps of atomic elemental distributions in biological specimens with a resolution approaching 2 nanometers. The facility will use software and instrumentation developed by the Group in collaboration with the computer systems laboratory, Division of Computer Research and Technology.

NMR Imaging Group

The Group has concluded its work in investigating the magnetic field strength dependence of nuclear magnetic resonance imaging. Because it is almost impossible to judge the performance of a system and the effects of an experiment on a patient simply by looking at images, a better way for estimating these attributes is badly needed. The Group proposed and carried out a series of experiments for this purpose. The method is based on bench measurements of the signal-to-noise ratio of the radio-frequency (rf) probes (transmitter/receiver) over the commonly used frequency range 1-100 MHZ. For this method to work properly, it is necessary to construct a carefully calibrated sense coil and conduct the experiment with properly matched and tuned probes. The group concluded that as long as multiple 180 degree rf pulses are employed for imaging, as they are now, then power deposition is a major factor in restricting the use of high field strengths, especially for body imaging, if reasonable safety guidelines are to be followed. The group also examined the complications brought about by chemical-shift artifacts.

The Group continued its work on the rotating-frame imaging method; here a special rf coil carries a gradient field when pulsed, in addition to the gradient imposed upon the main field. The probe for 3D imaging contains three sets of coils. They have to be arranged for easy placement and removal of the experimental object and, above all, they have to be electrically orthogonal, i.e., have no interactions among them. The Group has devised circuits to stop or minimize the interactions effectively, by using PIN diode switches, and has achieved independent tuning and matching for each probe section.

Scientific Equipment Services

Scientific Equipment Services (SES) provides instrument fabrication, repair and rental services to the NIH scientific community. During the last few years SES has implemented a number of new programs aimed at reducing job turn-around time, reducing costs and providing new services.

Reductions in turn-around time can be accomplished by assuring that SES responds to requests for service in a timely manner and that technicians can readily obtain the tools and supplies they need to complete a job. A new on-line computerized job control system will become operational in FY 87, which will permit rapid review of all jobs to assure that they are promptly assigned to a technician. New procedures have been instituted, too, in our purchasing department and stockroom to assure that needed items are available.

A number of new initiatives have been suggested by SES employees and the SES productivity committee, which will reduce the cost of providing our services:

- *Periodic Change of Vacuum Pump Oil:* A cart-mounted oil change system is being designed and fabricated that will permit rapid changing of the oil in vacuum pumps. This pump will be used in a program to routinely change oil in the vacuum pumps in research laboratories. Oil change time is estimated at less than ten minutes. Implementation of this system should result in a reduction of pump breakdowns and extend years of service.
- *Technicians' Personal Supply of Tools:* An analysis of the time needed for technicians to walk to the tool room to obtain tools found that it would be cost effective to permanently

supply each technician with many of the tools previously stocked only in the tool room. This will now be done.

- *Rental Delivery and Pick Up Board:* The rental program posts a list of instruments to be delivered and picked up. Technicians going to buildings on service call will review this list to determine if any rental equipment is to be delivered to those buildings. This procedure will eliminate many separate trips.

Three additional initiatives are a 'Loaner Program,' which will lend equipment to researchers while their instruments are being repaired; a 'Decal Service,' which will provide researchers with decals to put on selected instruments detailing proper operating and preventive maintenance procedures; and co-sponsorship with manufacturers of seminars and tutorials on the state-of-the-art of scientific equipment.

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Carolyn P. Brown, Chief, Library Branch, DRS, with the NIH Library Section Chiefs. *Left to right:* Lisa C. Wu, Technical Services Section; Maxine K. Hanke, Deputy Chief; Elsie Cerutti, Reference and Bibliographic Services Section; Rosalie Holmes Stroman, Readers Services Section.

Library Branch

Carolyn Brown, Chief

For the Library, the past year has been one of consolidating and refining the conversion to a new automated system. Staff tasks have gradually changed and new procedures are being adopted. Adjustments in software and hardware have been necessary as various phases of the automation plan are implemented; adjustments in timehonored methods and customs have had to follow as these become obsolete. Attention to technology or software newly available has yielded benefits. Without significant milestones, the year has been marked by slow steady improvements and by planning for future enhancements of the existing computer configuration.

Technological Improvements

One major adjustment which has decreased labor for data entry is the creation of a computer interface between the online catalog and the Library's long-term remote serials control system. The interface makes possible the transfer of data which have been entered into the serials system to the online catalog without further human intervention.

Another improvement was the acquisition of a software package to use with the interlibrary loan system. The system allows borrowers to request material they need from a library that owns it through an electronic message center. Lenders can signal through the same center that they will be able to lend the material. The new software enhancement permits the attendant to make a number of entries at once and leave the machine. Entries and responses are batched and updated automatically; requests from other libraries are batched and printed automatically. Approximately one hour of staff time is saved daily.

Usage data from the automated system have made a valuable contribution to the administration of the Library's collection. A constant evaluative process is necessary to remove less-used items and make room for new material coming in. Shifts in usage patterns can be monitored by checking the titles photocopied; low use rates continuing over months make the title a candidate for cancellation. During the year, the Library studied usage of its approximately 200 journal titles with two subscriptions. The resulting data showed that 65 titles were not photocopied frequently enough to justify the second subscription. The second subscriptions to these titles were cancelled for a saving of $16,000. Part of this money is to be diverted to orders of three subscriptions of a few extremely popular titles, and to second subscriptions of other popular titles.

Reserve book requests have increased notably under the new computer system. When a staff member requests a book that is charged out to another staff member, the system issues a recall the day after the due date for the requested book. A hold is placed on the borrower's right to borrow other books until that book is returned. NIH staff can now rely with much more certainty on getting a reserved book within a short time, since borrowers respond with greater rapidity now that they realize that failure to respond brings immediate sanctions. The use of reserve book requests has expanded, as has the use of the collection, with more people reading a new book while it is new.

Like other organizations using computers, the Library has begun to dispense with centralized services where feasible and use microcomputers to perform some functions. Microcomputers are now in evidence throughout the Library, and special programs are being run to avoid the delays and the expense of using large distant computers. Considerable savings have already been realized in removing large accounting and library files from central computers.

Education

The widespread use of microcomputers throughout NIH has provided the stimulus for a stronger and more diversified program of user education. The Reference and Bibliographic Services Section gave ten classes of "MEDLINE for the Health Professional," all booked to capacity. For advanced MEDLINE users, the Library began a monthly luncheon series of trouble-shooting sessions and advisory discussions. Library staff also initiated a program of visits to laboratories which have Medline codes to teach interested laboratory staff the rudiments of Medline searching.

Knowing the need at NIH for microcomputer software for bibliographic management, the Library sponsored several information technology programs featuring such software. It also sponsored instruction in searching of other than MEDLINE databases. Such classes have not reduced the search load for the search analyst staff. The number of searches performed during the year shows a modest 3 percent increase.

Service Enhancement

A new feature in the search service is the contract with Chemical Abstracts Service for access to their chemical structure file. This file is especially helpful in searching the chemical literature if the requester is uncertain of chemical nomenclaure or believes he has a novel compound.

Another new service offered is the production of bibliographies to be distributed after the talks at the Clinical Center's Grand Rounds series. Speakers define the subject of the bibliography and it is produced in time for them to edit it before the Grand Rounds presentation.

Improvements in established services continue to be made. The number of requests for loans and photocopies increased 20 percent in 1986 over 1985. Processing time continued to improve: 89 percent of all requests are completed by day 2 and 95 percent by day 3, as compared to 71 percent and 87 percent, respectively, in 1985. The Interlibrary Loan Unit borrowed 9 percent more than in 1985.

The Translation Unit has gained a wider clientele. The Surgeon General of the United States and the President's Council on Physical Fitness joined its users.

The Photocopy Service Unit had 12 percent fewer service calls for the photocopy machines and 41 percent less inoperable time because of machine malfunction. This is an average of all machines. The improvement is attributed to better preventive maintenance, better monitoring by the Library staff, and more attention from the companies servicing the machines.

After a test period of several months, during which information on how to access the Library's computer by telephone was given to an interested few, telephone access to the NIH Library catalog was opened to all of NIH. Instructions for setting terminals and for dialing in are issued to any NIH staff member who asks for them, along with the guide to searching the catalog which is available beside every terminal in the Library. Users are urged to read the guide thoroughly before attempting access. Many users, of course, are already familiar with the guide through using terminals in the Library.

Collection Review

The review of library journal subscriptions by subject has continued. Groups of specialists from the NIH research community participate along with one of the subject specialists in the library. At the end of the year a total of 725 titles had been reviewed. Eighty-two titles were cancelled as a result, with a total saving of approximately $8000. This amounts to about 8 percent of the total cost of the journals reviewed.

Future Plans

At the end of the year, the Library was preparing to acquire the computer equipment necessary to support a second-generation online catalog. The new catalog will be a considerable improvement in the sophistication of its search language, and requires additional computer power and an alteration to the computer room facilities.

Publications

Crump, Ted: Scientific/technical translation in a research library. *Reference Librarian*, in press.

Services of the NIH Library

The NIH Library offers a full array of services to assist scientific investigators in their work. They include:

- **Computer Bibliographic Searches** - Technical specialists perform computerized literature searches and compile bibliographies upon request. The staff is experienced in retrieving citations and abstracts from some 155 scientific databases. (Request from Reference and Bibliographic Services.)
- **Current Awareness Service** - The Library's Selective Dissemination of information (SD) program provides users with regular computer updates on new literature in the biological and medical sciences. (Request from Reference and Bibliographic Services.)
- **Reference Services** - Reference librarians not only answer reference questions on site or by telephone (496-2184), but also advise users of other library services that may meet their needs.
- **Photocopying** - Copy machines are available to users in a self-service area. (Photocopy Service, lower level.) The Library also will locate and copy articles upon request. (Request for at Circulation Desk.)
- **Microfilm and Microfiche** - Many journals are also kept in microform. Most are backfiles of important titles, acquired in order to save space. Reader-printers are reached through the Photocopy Service.
- **Circulation** - Books other than reference works and noncirculating reserve items can be checked out. Second copies of some of the most popular journals are also available for circulation.
- **Interlibrary loans** - Research publications not in the collection can be obtained from other libraries. Photocopies of journal articles obtained from the National Library of Medicine are usually provided in one to two workdays.
- **Translations** - Foreign language scientific materials are translated upon request from NIH staff. All translations are made available to other users.
- **Stacks Service** - Library staff will search for any volume a user cannot find on the shelves. (Request form at Circulation Desk.)
- **Publications** - "Recent Additions to the NIH Library" is available monthly in printed form and on the NIH WYLBUR computer system. "Current and Noncurrent Journals: NIH Library" is published biannually. Copies are available from the Circulation Desk.
- **Library Tours** - A tour providing an overview of NIH Library services and policies is avail able every Wednesday at 2 p.m., beginning from the Reference Assistance Desk.
- **Carrels** - Private study carrels are available on a limited, first-come basis. (Circulation Unit.)
- **Instruction** - Instruction on the use of the NIH Library and the automated catalog is offered periodically. "MEDLINE for the Health Professional" is taught monthly. (Further information available from Reference and Bibliographic Services.)
- **NIH Library . . . in Brief** - This eight-page Library guide is available upon request at the Circulation Desk.
- **Information Sheets** - One-page information sheets on specific services are available at the Circulation Desk.

Ron Winterrowd, Chief, Medical Arts and Photography Branch, DRS, with MAPB's Section Chiefs and staff, Office of the Chief. *Front row, l to r:* B.J. Collier, Administrative Officer; Howard Bartner, Medical Illustration Section; Mr. Winterrowd. *Second row:* Lorie Battle, Secretary; Pat Lewis, Graphics Section; Linda Brown, Design Section; Edward L. Singleterry, Photography Section.

Medical Arts and Photography Branch

Ronald B. Winterrowd, Chief

The Medical Arts and Photography Branch is a central service organization providing the NIH community with comprehensive visual communication services. MAPB's products, in a wide variety of media, visually express scientific data, research accomplishments, and NIH programs in publications and oral presentations for the scientific community and the general public.

The Branch's staff of professional artists, photographers, and other specialists have extensive expertise in converting data into effective presentations. They are highly skilled in meeting the needs of scientists for graphic presentation, medical arts, and still and motion picture photography, including photomacrography and photomicrography. Services include design and production of publications; preparation of slides, vugraphs, and other projected visual aids; exhibit design; statistical drafting, display charts; posters; and medical illustrations.

The philosophy of the Branch is to provide high quality professional services competitive in cost with commercially obtainable services. To this end, the staff works closely with vendors of design, graphics, and photography services to ensure the requestors' needs are met and that MAPB's quality standards are maintained.

During FY-86, MAPB made a successful transition to total funding under the Service and Supply Fund which was mandated under the NIH full cost recovery initiative. In addition, the Branch began the implementation of a computerized Job Tracking and Control System to provide quick, reliable information on job status, cost, use of MAPB services, and overall productivity. Once the system is in place, MAPB will be able to provide the institutes with information on individual user requests and costs.

The Branch continued sending a team of staff members to NIH laboratories and other units to explain its services, inform users of cost-saving measures and obtain suggestions on how services can be improved. Units in every Bureau, Institute, and Division have been visited, and MAPB wishes to remind its users that staff will gladly visit any NIH unit, no matter how small, for an information exchange.

Demand for MAPB services continued to be high and constant, although some decrease in service requests was experienced during late spring and early summer because of budgetary restraints within the institutes. In order to accommodate the volume and diversity of services requested by the NIH community, MAPB utilizes the services of a wide variety of small and minority businesses in the Washington metropolitan area. To reduce costs to the requestor, MAPB requires competition among qualified vendors for many jobs, and daily bid sessions are held for all graphics job requests.

Photography Section

The number of jobs received in the Photography Section increased by 8 percent. However, the number of production units decreased by 2.5 percent, as a result of cutbacks in the Institutes and of cost saving measure encouraged by the section.

The Section installed IBM-PC computers in order to have more current access to data as required by the BIDs for better control of the use of the service and for budget planning.

The Photography Section continues to supplement in-house photographic laboratory services by obtaining services of private photographic facilities in the Washington, D.C., area.

Design Section

The Design Section is composed of a group of professionally trained, highly skilled, and experienced designers. Many have won awards in local, national, and international art competitions. The section provides the NIH community with design services both for scientific presentations and for public information. This includes publications, posters, editorial and technical illustrations, and slide shows, as well as design and preparation of support materials for various conferences organized at NIH. In FY 1987, the Design Section continued to experience a high demand for services, although some decrease in job requests was noted during the early summer due to budgetary restraints within the institutes.

Graphics Section

The Graphics Section, composed of professionally trained, highly skilled and experienced illustrators and visual information specialists, provides the NIH scientific community with graphic art for scientific presentations and public information; this includes illustrations, posters, charts, graphs, tables, slides, and

computer generated graphics, as well as the design and preparation of support materials for various conferences organized at NIH. The volume of requests for service remained high, although slightly decreased during the latter part of FY-86. The Graphics Section continues its efforts to reduce costs, and daily bid sessions are held with various private sector vendors to reduce costs through competition.

The Graphics Section is planning implementation of an in-house state-of-the-art computer system that will produce charts, graphs, tables, text slides, etc., with the goal of reducing costs to BIDs without reduction in quality. The system will be operational in FY-87.

Motion Picture and Special Events Unit

The professional staff of this unit provide (1) motion picture services of cinematography, sound recordings, editing, and related laboratory services; (2) medical and scientific videotaping services; and (3) services for all special events, including poster presentation, slide shows, exhibits, Congressional and VIP presentations, Medicine for the Layman lectures, and signage system design and production.

Medical Illustration Section

The Medical Illustration Section produced a wide variety of black-and-white and color medical illustrations and diagrams of surgical, gross pathological, ophthalmological, biological, and dental subjects. During FY-86, the section became more involved with public information projects; medical illustrations were utilized in poster design as well as for reproduction in public information brochures.

Medical illustrations are requested to described complex medical and surgical procedures when other means of reproduction would not provide the detail required. Long hours of surgical observation, research, and planning are usually necessary before initiation of many projects; extensive knowledge of human anatomy and of artistic techniques and applications is required.

Outlook for FY 1987

MAPB will continue its efforts to provide its clients with high quality service at the lowest possible cost through continued competition among MAPB vendors, increased in-house productivity, and informing clients of ways they can reduce costs for job requests. The implementation of the Branch's computerized Job Tracking and Control System will be completed in FY-87, which will benefit both MAPB and the NIH community by providing detailed information on job requests and costs.

Dr. Stephen Potkay, Chief, Veterinary Resources Branch, DRS, with the VRB Section Chiefs. *Left to right:* Dr. James F. Harwell, Jr., Veterinary Medicine and Surgery Section; Dr. Francis Judge, Animal Center Section; Dr. Anton M. Allen, Comparative Pathology Section; Dr. William T. Watson, Small Animal Section.

Veterinary Resources Branch

Stephen Potkay, V.M.D., Chief

The Veterinary Resources Branch (VRB) provides professional and technical support service for NIH intramural programs. It is responsible for:

- Production of defined research animals
- Procurement, quarantine, conditioning, and issuance of animals from outside sources
- Management of a central animal surgery and radiology facility
- Animal disease diagnosis and control
- Research holding for primates, cats, dogs, rodents, and livestock
- Consultative services on animal health, care, husbandry, genetics, and nutrition
- Maintenance of an international laboratory animal Genetic Resource
- Administrative support of the Interagency Research Animal Committee and NIH Animal Research Committee.

The Branch met these responsibilities and extended its efforts in assessing its services and their utility to the NIH. This assessment was closely related to the declared intent of the NIH to achieve accreditability by the American Association for Accreditation of Laboratory Animal Care (AAALAC) by October 1987, and included developing plans whereby VRB's facilities and resources could be used most effectively in achieving this goal.

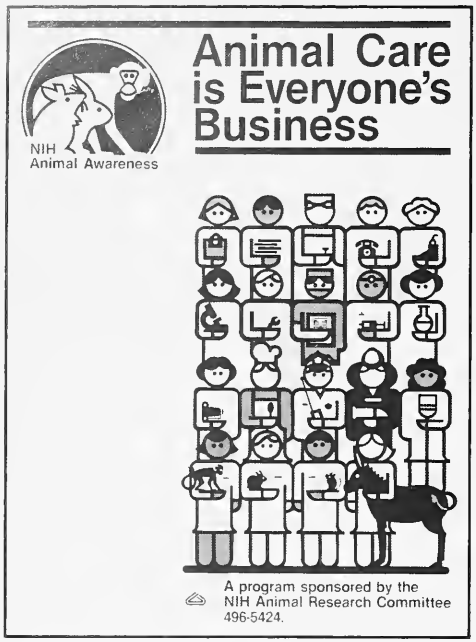
The implementation of full cost recovery accounting had a significant, and largely negative, impact on certain VRB service and supply fund activities. Evaluations of the affected Program areas—undertaken in anticipation of these events—were concluded and implementation of corrective measures was begun; specific actions are described under the section activities which follow.

Ongoing administrative support continued to be provided to the Interagency Research Animal Committee (IRAC) and the NIH Animal Research Committee (NIHARC). During this period of increased public concern about the use of animals in biomedical research, testing, and training, the IRAC provided leadership for development of policies and oversight for Federal programs regarding the use of experimental animals. Most Federal agencies have adopted uniform policies on animal care and use modeled after the recently revised PHS Policy on Humane Care and Use of Laboratory Animals, which includes the Principles for the Utilization and Care of Vertebate Animals used in Testing, Rsearch, and Training. These Principles were developed by IRAC at the request of the Office of Science and Technology Police.

Major Federal legislation on animal care and use was enacted during the year, and IRAC provided recommendations to the U.S. Department of Agriculture about the regulations which USDA will adopt to implement the new legal requirements. IRAC continued to provide an official U.S. Observer to the Council of Europe's Ad Hoc Committee for the Protection of Animals in Research (CAHPA), which is currently developing a Convention on Animal Transportation. This subject is of considerable interest, since, even within the United States, many regulations on the subject are confusing or conflicting, and for some species there are no regulations. IRAC maintained contact with those Federal agencies having responsibilities in this area, as well as with the International Air Transportation Association and CAHPA, in an effort to achieve a single policy on the transportation of laboratory animals that would be workable on an international basis. Monitoring of foreign and domestic supplies of nonhuman primates and their use in research continued, as did IRAC's work with the Pan American Health Organization to develop national primate plans designed to preserve wild populations and provide monkeys for biomedical research.

A major accomplishment of the NIH Animal Research Committee this year was the launching of an Animal Awareness Program at the NIH. It consists of a series of posters placed in each building conveying some theme about animal care. The initial poster, captioned "Animal Care is Everyone's Business," was well received by NIH employees and visitors. The program will be used to provide video presentations and lectures to NIH employees and facilitate communication on issues relevant to animal care and use (Figure 1). The NIHARC became increasingly involved with the NIH commitment to become entirely AAALAC-accredited and with implementing decisions of the Animal Research Committees of the NIH Bureaus, Institutes, and Divisions (BIDs). Guidelines were developed to ensure consistency between BIDs regarding submission of the USDA Animal Report. In addition, a subcommittee was formed to draft intramural guidelines on the use of Freund's adjuvant and other research practices in animals.

Figure 1
First Poster for NIH Animal Awareness Program



The beneficial effects of animals on human health and well-being is an area of continuing interest to VRB. A small pilot program was initiated in the play room of the Clinical Center this year, and an NIH conference on the subject is planned for 1987 to help raise the state of science in this emerging field.

Animal Center Section

The Animal Center Section (ACS), located in Poolesville, Maryland, acquires, issues, maintains, and develops large laboratory animal models and provides related services and products for NIH investigators. The animals involved are primates, farm animals, and dogs and cats. Of these, monkeys, miniature swine and dogs are provided by breeding colonies.

The principal mission of the Primate Unit—long-term primate research holding—continued unchanged, with project support being given to the National Cancer Institute (NCI), the National Institute of Child Health and Human Development (NICHD), the National Institute on Aging (NIA), and the U.S. Army Medical Research Institute for Infectious Diseases. A study initiated last year by the Food and Drug Administration (FDA) to evaluate lipid-rich diets in *Cebus* monkeys was successfully concluded. In its place, a major project was begun by the NIA to determine the effects of dietary restriction on the longevity of rhesus and squirrel monkeys. The project will eventually involve some 200 monkeys and require over ten years to complete. Overall numbers of nonhuman primates acquired, quarantined and issued, however, continued to decline—a trend which is expected to continue.

The rhesus breeding colony managed under contract by the University of Miami in Perrine, Florida, was sold intact to the Primate Research Institute in Alamogordo, New Mexico. Terms of the sale included a provision to supply rhesus monkeys to the NIH, with first priority given to the National Institute of Mental Health (NIMH) for males in accordance with its specified needs and financial commitment. A contract was also awarded to supplement NIH's requirements for rhesus and cynomolgus monkeys, particularly those for male rhesus monkeys.

Fifteen macaques, housed at the Primate Unit and provided with veterinary care at the request of the Montgomery County Circuit Court after their seizure by the State in 1981, were relocated to the Delta Regional Primate Center in Covington, Louisiana.

There was a significant decrease in the number of all species of animals maintained by the Ungulate Unit with the exception of swine. The NCI herd—designated the Swine Leukocyte Antigen (SLA) inbred miniature pig—continued to be maintained at approximately 275 head. As a result of culling and selection based on reproductive performance, the breeding population of 65 sows was reduced to 35 without a loss in production; the smaller group is easier and more efficient to manage. Excess stock was provided to the USDA, a veterinary college, and a research hospital. Although the National Heart, Lung and Blood Institute (NHLBI) continued to use lambs to study artificial heart valves, the numbers have declined markedly, and the amount of normal sheep blood issued to support the project dropped approximately 60 percent. Miniature swine being used in an NHLBI atheriosclerosis study were reduced from 25 to 12 head.

Canine programs, particularly breeding, continued to undergo significant change (Figure 2). Foxhound breeding was discontinued midway through the year because of NHLBI program changes which will require few dogs in the future. Breeding of pointers for the NIMH was temporarily suspended when it was found that a number of breeders had audio-visual deficits which could interfere with antianxiety drug testing in them or their progeny. The breeding and raising of beagles for the NCI was almost completely phased out during the year. Holding

of beagles for the NEI, however, continued. Their use in studies involving diabetic retinal degeneration progressed well, with the support of Carnivore Unit personnel.

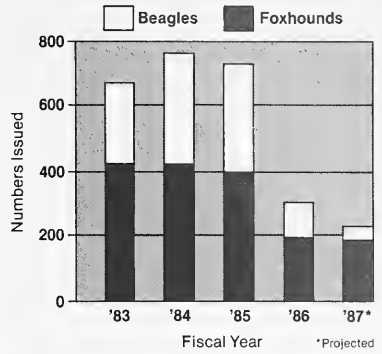
A variety of collaborative research projects were conducted at the Animal Center. Those involving primates included work with scientists of NICHD and the Uniformed Services University of the Health Sciences (USUHS) to correlate progesterone receptor activity and cortisol levels with reproduction in squirrel monkeys. The influence of light on reproduction in New and Old World primates, and the effects of hippocampal lesions on rhesus monkey behavior were areas of study undertaken in support of NIMH and NICHD investigators. Efforts to better understand husbandry requirements and enhance the productivity of owl monkeys (*Aotus trivirgatus* and *A. vociferans*) were continued on behalf of NICHD and the National Institute of Allergy and Infectious Diseases (NIAID). These species are of particular importance in ophthalmologic studies and malariology. NICHD research involving behavior and vocalization in squirrel monkeys (*Saimiri* sp.), as they relate to human infant development, were also supported. Several projects were continued in collaboration with investigators from Clemson University, the Smithsonian Institution, and USUHS involving estrus synchronization, embryo transfer and cystic endometrial hyperplasia in SLA swine. Efforts also continued to establish a flock of sheep homozygous for hyperbilirubinemia. Finally, the use of tolainide HCl to determine its antiarrhythmic effects during hypothermia induction and rapid rewarming was studied in beagles with the collaboration of FDA and Virginia Polytechnic Institute investigators.

Veterinary Medicine and Surgery Section

The Veterinary Medicine and Surgery Section (VMSS), provides centralized facilities for experimental surgery and research animal holding, and offers routine care and comprehensive veterinary support for the animals maintained there. It also gives consultative and other assistance to BID scientists concerning the development and use of laboratory animals.

The Surgery Unit (SU), which offers expertise and an optimal environment for aseptic surgery, handled more than 1000 cases—a number that has been constant over the past several years. Substantial support was provided to the NEI for its studies of alloxan-induced diabetic retinopathy, and efforts continued to be directed toward supporting an NHLBI project to evaluate methods for effecting myocardial neovascularization as a treatment for infraction. A variety of new projects were undertaken to meet BID research needs in areas such as the pharmacology of antineoplastic agents, the pathophysiology of focal cerebral ischemia, neural cell transplantation in the treatment of hemiparkinsonism, and the evaluation of new bone graft substances.

Figure 2
Issues of Research Dogs



The Comparative Medicine Unit (CMU) implemented several significant operational changes which resulted in expanding its technical support role. Such services were provided in support of NCI studies of laser treatment for prostatic hypertrophy, and the pre- and postoperative care of swine used to develop and refine bone marrow transplantation techniques. The Unit also continued to accommodate long term NCI investigations of the effects of radiation therapy on the peripheral nervous system, as well as NIMH studies of Parkinsonism, both of which utilized dogs as the experimental model. Research holding was at a substantially lower rate than in the past, due largely to a de-emphasis of research involving dogs by the NHLBI (Figure 3). Efforts were well under way to continue upgrading the holding facilities for hoofed stock by installing flooring material suitable for these species and improving ventilation.

About 850 nonhuman primates representing eight species were maintained by the Primate Research Unit (PRU); they were used in 25 BID research projects. The primate recycle program, which is operated as means of conserving these valuable species, issued more than 40 monkeys. Considerable effort was expended in adapting the Unit's operating procedures to meet increased BID requirements for specialized technical support and holding facilities. For example, space was made available to permit the NHLBI to relocate all of its primate activites

in the Unit, a move that was consistent with NIH's accreditation efforts. Investigators from other BIDs were also assisted through the provision of more adequate work space in proximity to the primate colonies so as to improve their research efficiency.

Small Animal Section

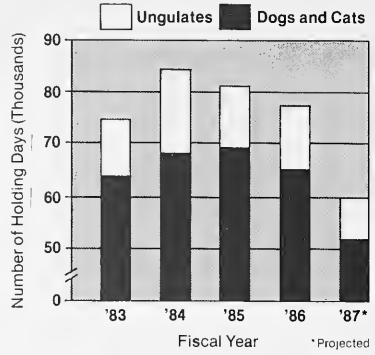
The Small Animal Section (SAS) provides rodents and rabbits from its production colonies and also manages contracts for this purpose. It manages the NIH Animal Genetic Resource (NIHAGR) containing more than 250 defined strains and stocks, and has programs devoted to animal model development, nutrition, health, embryo cryopreservation, and research holding.

Approximately 554,763 animals were issued, which is an 18 percent decrease from last year. The total represents 138,691 in-house and 416,072 contract issues (Figure 4). This dramatic decrease was due largely to economic pressures within the BIDs to control expenditures. BID concerns in the financial arena were also reflected by the numerous inquiries received concerning billing procedures and investigator accounts. In an effort to be of assistance, internal procedures were developed to provide total estimated costs, including those for delivery, so that investigators could consider these before purchasing animals. In addition, negotiations with contract suppliers resulted in the provision of some animals at reduced cost. The delivery of animals at the NIH was carefully reviewed and guidelines were implemented to increase efficiency and ensure the security of animals delivered, whether from commercial or in-house sources.

The mission of SAS was examined in detail during the year, and it was concluded that the interests of the NIH research community could best be served by redirecting SAS resources towards providing and supporting research holding activities. This will require a further decrease in in-house animal production and the reallocation of personnel and space. Along these lines, several mouse and rat production colonies were discontinued and comparable animals were supplied through contracts managed by the Division of Cancer Treatment, NCI. The remaining SAS production is focused on providing investigators with unique or hard-to-raise animals in limited quantities. Specifications were developed to staff some of the equipment sanitation activities through a contract at a later date, and provision was made to permit contract expansion to accommodate BID needs for such services elsewhere on campus.

As in past years, the major changes in the composition of the NIH Animal Genetic Resource resulted primarily from undertaking

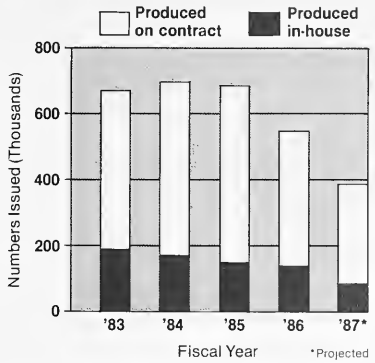
Figure 3
Large Research Animal Holding—Bethesda



new projects at the request of the BIDs. One new mouse strain, Non Obese Diabetes (NOD), and one new rat mutant, myelin deficient (*md*), were established from outside sources. A rat mutant, pigeon toe (*pt*), was discovered in the colony and established. Principal efforts involving mice dealt with immunocompromised congenics. Development was completed on the NFS/N-*me-Xid* and NFS/N-*nu-me* combinations, and the first step in forming the NFS/N-*me-Xid-nu* was finished. Work was begun on developing the C3H/HeN-*me-Xid*, and the C57BL/6N-*bg-nu-XID* triple deficient model was completed, although the latter will not become routinely available for about a year. Interest in these mice stems from the fact that they are devoid of lymphokineactivating killer (LAK) cells, which are thought to provide the primary immunological defense against tumor cells. A marked interest in the motheaten (*me*) mutant has developed, and the demand is beginning to exceed the capability to produce them.

Progress continued in further defining the rat model for insulin independent diabetes. It was determined that the SHR/N strain expresses this disease at an older age than its congenic counterpart which is homozygous for the corpulent gene (*cp*), suggesting that obesity may accelerate the expression of frank diabetes in animals that are genetically predisposed. Progress continued in establishing the nude (*rnu*) gene in a number of inbred strain backgrounds. It has been established through this model that T lymphocytes play a critical role in bringing about and maintaining the inflammatory processes in induced rheumatoid arthritis, since normally susceptible rats do not exhibit the disease when homozygous for the nude gene.

Figure 4
Rodents and Rabbits Issued



Toothless (*tl*) and osteopetrosis (*op*) genes were established in the F344/N and LEW/SsN strains, and limited production will be undertaken. Studies were also undertaken to determine the cause of the marked differences between rats homozygous for the jaundice (*j*) gene in the ACI/N and RHA/N strains. With the completion of inbreeding, the cotton rat (*Sigmodon hispidus hispidus*) was established as an inbred strain. Interest by the biomedical research community in the Watanabe rabbit, a model for familial hypercholesterolemia, was considerable. A major effort was undertaken to improve its reproductive performance and provide a higher quality animal for issue. Profiles for blood cholesterol and triglycerides on the colony were established, protocols for colony management were improved, and studies were designed to establish the dietary requirements of this rabbit.

The embryo cryoperservation program (ECP) continued to provide new technology to improve the management of the NIHAGR. More than 36,700 embryos were collected from 34 stocks and strains of mice, and over 8035 embryos from 12 new genotypes were added to the frozen genetic store. Others were used in studies designed to improve techniques and program efficiency. The overall survival rate of frozen-thawed embryos was 58 percent, and efforts to improve their *in vivo* survival following transfer into recipient females continued. Studies were also initiated to evaluate the feasibility of banking rabbit embryos to allow reduction or elimination of the allotype and C6 deficient rabbit colonies. Superovulation and mating regimens and collection schedules were established, and it was acertained that propylene glycol is the cryoprotectant of choice for embryos of this species. The influence of freezing variables on *in vitro* development is currently being investigated, and embryo transfer procedures will be developed as embryo survival rates improve.

Most of the nutrition program's research activities involved collaborative studies with BID scientists. Research on diet development was limited to that involving nonhuman primates and the Watanabe rabbit; the recently developed marmoset diet has been included as an NIH stock item. Assistance and advice in designing and conducting experiments with nutritional elements were provided to investigators at NIH and elsewhere in the biomedical research community. A workshop on diets for rodents used in chemical carcinogenicity studies was conducted with the National Institute of Environmental Health Sciences (NIEHS), and information on new diet development and quality assurance procedures was provided to the U.S. Navy in Cario, Egypt, and to the National Aeronautics and Space Administration. The nutritionist continued to be active on the NIH Nutrition Coordinating Committee (NCC), and participated in the two workshops sponsored by the NCC this year. Problems regarding the quality of diets procured for use at NIH have been practically nonexistent.

Outbreaks of Kilham's rat virus (KRV) and Theiler's mouse encephalomyelitis virus (GD VII) infections, and unexplained neonatal deaths were the major concerns in the animal health program. The occurrence of KRV necessitated destruction of all rat production colonies. GD VII, detected serologically in two barrier rooms, was not associated with clinical signs, and measures for its control and for depopulation and rederivation of the animals were considered impractical. Users were notified that rederivation would be deferred until the completion of new barrier facilities scheduled for 1988. Neonatal deaths in the rabbit and guinea pig colonies continue to be of concern, but causative or contributing factors have not yet been identified. Microbiological contamination in the barrier appeared to be increasing; isolates included *Proteus* sp, *Corynebacterium* sp, *Klebsiella* sp, and unidentified gram positive cocci. Monitoring of the cagewashers and autoclaves indicates that contamination is occurring on the 'clean' side, and increased attention has been given to enforcing showering techniques, since many of the isolates are typical human flora. *Bacillus piliformis* titers were detected in the N:OM rat colonies; the infection was eliminated during the depopulation measures taken to eradicate KRV.

Eighty-six investigators from 12 BIDs and the FDA used the rodent research holding service. Their activities increased steadily through the

first half of the year, but a sharp decline occurred during the remainder as a result of BID budgetary reductions. Two rooms were renovated and subdivided into four to better serve investigator needs by allowing fewer and smaller projects in these areas. The gnotobiotics staff performed 80 hysterectomies for the NIHAGR, of which 71 were successful. Nineteen mouse litters and 12 rat litters of different stocks and strains were sent to contractors and medical schools.

Comparative Pathology Section

The Comparative Pathology Section (CPS) characterizes and improves the health status and studies naturally occurring diseases of laboratory animals which are produced, quarantined, or utilized at the NIH. Through its genetic investigation and monitoring program, it assures the genetic quality of animals provided by NIH for use as breeders to other institutions throughout the world. It also provides an Animal Disease Investigation (ADI) Service which offers diagnostic services, consultation and advice to the BIDs on animal colony management.

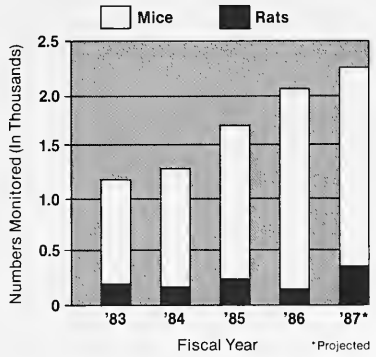
Reductions in rodent production activities and the absence of major disease outbreaks at the NIH were responsible for a 20 percent decline in the number (3833) of necropsies performed by the pathology service, compared to last year. Deaths in the different species were caused by a variety of miscellaneous conditions, and, as in the past years, large numbers of guinea pigs and rabbits were stillborn (fetal atelectasis). Although cecitis in rabbits remained a significant problem, there were no massive outbreaks. Many necropsies were performed for NIH investigators through the ADI Service; the animals suffered from a variety of disease problems in holding facilities of the BID's as a result of pooling animals from diverse sources. Considerable assistance was also provided to BID investigators in distinguishing naturally occurring diseases from experimentally induced conditions.

The slight decline in the number of samples received by the clinical pathology service for endo-and ectoparasite monitoring, hematology, and contracted virus monitoring was attributed mainly to the elimination of various SAS Animal production colonies that were previously monitored, and decreased monitoring of certain contract production colonies known to have effective health programs. The number of samples received by the microbiology service for culture and serology increased slightly, due, in part, to the incorporation of routine mycoplasma culturing of mice received for health monitoring. This was precipitated by the occasional finding of low positive titers with the mouse mycoplasma ELISA. The ADI service responded to 330 calls for assistance from the BIDs. This is approximately 4 percent lower than in 1985, and is probably due to more clinical cases being handled by the BID veterinarians. In addition, there were no major disease outbreaks on the NIH campus.

Importation and quarantine services were provided to permit introduction of rodents and rodent products from non-approved sources into NIH so as to minimize the risk of introducing ectromelia, lymphocytic choriomeningitis, and Hantaan viruses. The number of such permits was 30, or 37 percent less than last year. Five required that rodents be quarantined in SAS facilities at Poolesville, 4 required quarantine by CPS, 9 were quarantine by the BIDs, and 12 did not require quarantine. Approximately 200 rats and 1850 mice from the NIHAGR were monitored for genetic integrity. This represents an increase of 18 percent, and constitutes the second consecutive year of substantial growth in the program (Figure 5). A feature of the program this year has been the number of requests involving verification of the congenicity of various strains. Growth was also a direct result of the expansion of programs which included the monitoring of congenic mouse strains being developed by the SAS as well as the monitoring of FI hybrid animals from the production colonies. To meet the increased workload, alternate monitoring methodologies were developed, including testing for a standard battery of markers using cellulose acetate electrophoresis rather than examining a critical subset of markers using starch gel electrophoresis. This approach also resulted in decreased administrative requirements in the areas of scheduling, record keeping and tissue storage. It is anticipated that the major program change for next year will be to initiate the monitoring of a large number of congenic rats being developed by the SAS. For a variety of reasons, the monitoring of rat strains is far more time consuming than for mouse strains, and relatively small increases in the number of rats being tested can result in a significant increase in total workload. No major genetic containations were reported or detected in any of the inbred lines maintained in the foundation colonies. A number of investigations were initiated, however, to resolve problems related to the mislabelling of animals within and outside of the Branch.

Research activities in CPS were concerned with studies of the pathogenesis of laboratory animal diseases, their control, and the development of methods to monitor for infectious agents and genetic integrity. Specific research activities involved development of genetic profiles for inbred laboratory mice and rats, further

Figure 5
Genetic Monitoring



studies on the pathogenesis of cilia-associated respiratory (CAR) bacillus infections, and investigation of an atypical *Escherichia coli* which caused diarrhea and death in N:NIH(s)III-*nu* mice.

Major adjustments in CPS programs are anticipated in order to accommodate projected changes in VRB and NIH activities. For example, the conversion from animal production to animal holding activities in VRB will alter the nature of the disease problems and workload to be handled. More importantly, a strong, coordinated animal health assurance plan must be evolved in order for the NIH animal program to be AAALAC accreditable, and this requires that BID veterinarians collaborate in its development. Requirements to be addressed include those for more comprehensive and rapid pathology services, NIH-wide microbiological monitoring of rodent colonies, and expanded, basic clinical pathologic services applicable to all laboratory animal species. Other issues to be addressed, in conjunction with SAS program areas, include centralizing and streamlining rodent importation and quarantine activities, as well as embryo cryopreservation and genetic monitoring as they pertain to BID needs for transgenic mice.

Forecast

A downward trend in the use of research animals, particularly those produced by VRB, is expected to continue into next year. Efforts will continue in redirecting the mission of affected programs from production to research holding, which is consistent with the principles of cost effectiveness and the needs of the NIH both while it seeks AAALAC accreditation and thereafter. To this end, renovation of one facility to accommodate known BID rodent holding requirements will be planned during the next year. It is anticipated that modernization of housing for the NIHAGR will be completed during the same period. The nature and scope of animal health and quarantine services provided by VRB will be fully evaluated in light of ongoing changes within the Branch and the need for NIH to have a comprehensive, yet unified, animal program in its quest for AAALAC accreditation. In the same vein, the need to provide accreditable facilities for miniature swine will be pursued. It is anticipated that the Branch, through the NIH Animal Research Committee, will continue to identify and propose solutions, and further enhance the sensitivity of the NIH community to issues involving animal care and use.

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